2250994b

Revision

Pharmacology :

It's the science (study , Knowledge) of drugs & their effect on human body.

Pharmacodynamics :

It studies the effect of drug on Living systems (human body). , Biochemichal , physiological conditions that affects the drug, M.O.A.

PharmacoKinetics :

It studies the action of body on drug including absorptn, , distributn, , Metabolism , excretion (ADME)

Nice sketch

Dose of Drug administered
↓ absorption
Drug conc. in Systemic circulatn, (Protein Bounded (inactive) ⇌ free (active))
- distributn, → drug in tissues
- eliminatn, → drug metabolized or, excreted.

} Kinetics

↕

Drug conc. at the site of actn, (↑ free drug in circulatn, → ↑ receptor Binding) → Pharmacological effect
- Toxicity
- Therapeutic

} dynamics

(*) Drug molecules interact é a special molecule in the Biological system that a regulatory role this Molecule is called "Receptors"

(*) Not all drugs act by receptor Binding such as :
(1) antacids
(2) Charcoal tabs → adsorption of intestinal gases
(3) Laxatives , diuretics

Receptor types :

(1) Agonist (Ligand) gated channels → made up of proteins Subunits forming central pore
examples : nicotinic & GABA receptors , glutamate

(2) G-protein coupled receptors → Form 2nd messenger
muscarinic R - norAdrenergic R - Dopamenergic R

(3) Kinase - Linked surface receptors → include receptors For insulin.

(4) Nuclear receptors for steroid , thyroid hormones in nucleus → regulating transcription & translation.
insulin - Histamine

و ممكن نرجع لل sketch في المحاضرة السابقة page (10)

و بصراحة إحنا لازم نرجع له و نبوس عليه كويس.

Pharmacodynamics :

بطريقة تانية

It's the study of relation between conc. of drug * & the response produced

* at the receptor.

(*) Magnitude of response is proportional to the no. of Complexes (Drug-receptor)

→ This is called (occupation theory or // Key & Lock)

effect {hyperbola}

E_{max}

0.5

EC_{50}

Conc. (at receptor site)

زودها على المحاضرة السابقة (مهمة)

taking Log Conc. →

effect {Sigmoidal}

max effect.

50%

Log Conc.

: Dose which give 50% response of Drug

والـ 2 curves دول طبيعاً من المحاضرة السابقة

receptor bound drug

أما الجديد

Binding max (B_{max})

0.5

K_D

conc.

خلي الـ curve ده في مخك وهنشرحه كمان شوية بالتفصيل المهل سه لا تقلق

$$*[D] + [R] \underset{k_2}{\overset{k_1}{\rightleftharpoons}} [DR] \longrightarrow \text{Response}$$

Forward Rx $Rate_1 = \frac{d[RD]}{dt} = k_1[D][R]$ → association Const

Backward Rx $Rate_2 = -\frac{d[DR]}{dt} = k_2[DR]$ → dissociation "

∴ At equilibrium $Rate_1 = Rate_2$

$$\therefore k_1[D][R] = k_2[DR]$$

~~association Rate Const.~~ ← $\frac{k_2}{k_1} = \frac{[D][R]}{[DR]} = k_D$ → equilibrium ~~distribution~~ Dissociation Const. → ①

Fractional occupancy ← $f = \frac{[DR]\ \text{complexes}}{[R]_{free} + [DR]\ \text{complexes}}$ → ②

from ① $k_D = \frac{[D][R]}{[DR]}$

$$\therefore [DR] = \frac{[D][R]}{k_D} \rightarrow ③$$

from ③ & ②

$$F = \frac{\frac{[D][R]}{k_D}}{[R] + \frac{[D][R]}{k_D}}$$

$$F = \frac{[D][R]}{k_D\left[[R] + \frac{[D][R]}{k_D}\right]}$$

$$F = \frac{[D][R]}{k_D[R] + [D][R]}$$

$$F = \frac{[D][R]}{[R]\left[k_D + [D]\right]}$$

$$F = \frac{[D]}{[D] + k_D}$$

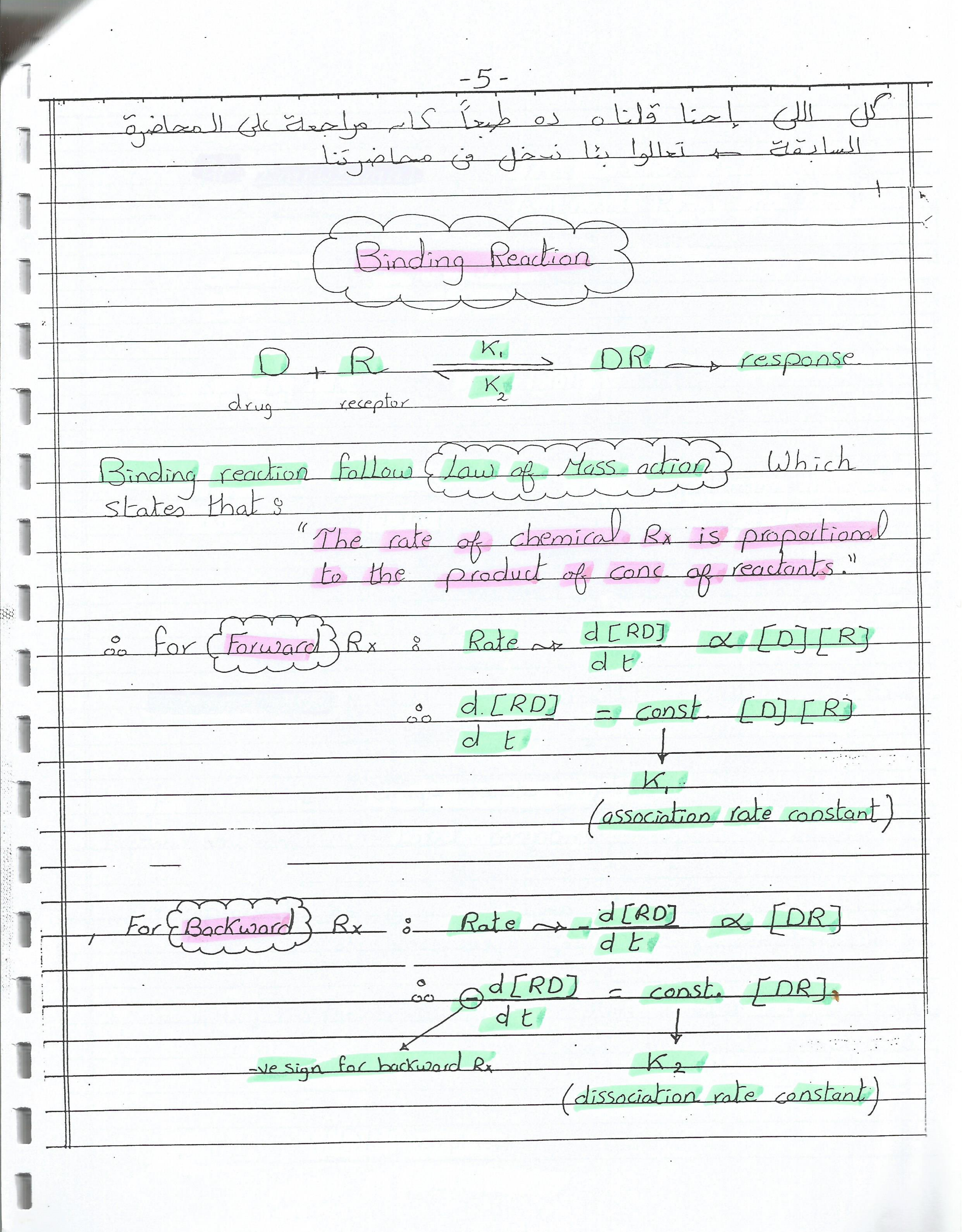
$$\therefore F = \frac{[DR]}{[R] + [DR]} = \frac{[D]}{[D] + k_D}$$

when $k_D = [D]$

$$\therefore F = \frac{[D]}{2[D]}$$

$$F = \frac{1}{2}$$

i.e Drug occupy 50% of Receptors



كل اللي إحنا قولناه ده طبعاً كان مراجعة على المحاضرة السابقة ← تعالوا بنا ندخل في محاضرتنا

Binding Reaction

$$D + R \underset{K_2}{\overset{K_1}{\rightleftharpoons}} DR \rightarrow \text{response}$$

(D = drug, R = receptor)

Binding reaction follow (Law of Mass action) Which states that :

"The rate of chemical Rx is proportional to the product of conc. of reactants."

∴ for (Forward) Rx : Rate → $\frac{d[RD]}{dt} \propto [D][R]$

∴ $\frac{d.[RD]}{dt} = \text{const.} [D][R]$

const. → K_1 (association rate constant)

, For (Backward) Rx : Rate → $-\frac{d[RD]}{dt} \propto [DR]$

∴ $-\frac{d[RD]}{dt} = \text{const.} [DR]$

(−) → -ve sign for backward Rx

const. → K_2 (dissociation rate constant)

(*) **At Equilibrium :** The 2 rates of Forward & Backward Rx(s) are equal.

$$\therefore \frac{d[RD]}{dt} = -\frac{d[DR]}{dt}$$

$$\therefore K_1 [D][R] = K_2 [DR]$$

$$\therefore \frac{K_2}{K_1} = \frac{[D][R]}{[DR]} = K_D$$ equilibrium dissociation constant.

مهم جداً

خليك ماشي معانا وهتعرف حالاً هو مهم ليه

إحنا بندرس كل ده علشان نعرف حاجة إسمها **fractional occupancy**

$$f = \frac{\text{drug - receptor complexes}}{\text{total receptors}}$$

fractional occupancy

يعني أنا أخدت drug معين مسك في بعض الـ receptors وعمل complexes و هناك بعض الـ receptors لسه free

إحنا بنشوف كمية الـ receptors اللي عملت complexes بالنسبة للـ total receptors اللي أصلاً موجودة.

$$\therefore f = \frac{[DR]\ \text{complexes}}{[R]_{\text{free}} + [DR]\ \text{complexes}}$$

ونكتب القانون الأخير ده تاني علشانه مهم وهنشتغل عليه دلوقتي

$$f = \frac{[DR]}{[R] + [DR]} = \frac{[D]}{[D] + K_D}$$

سبحان الله جه منين ده تعالوا نشوف Mathematical derivation

We said that :

$$K_D = \frac{[R][D]}{[DR]}$$

$$\therefore [DR] = \frac{[R][D]}{K_D} \longrightarrow (1)$$

, We said that :

$$f = \frac{[DR]}{[R] + [DR]} \longrightarrow (2)$$

→ By Substituting From (1) in (2)

$$\therefore f = \frac{\frac{[R] \times [D]}{K_D}}{[R] + \frac{[R] \times [D]}{K_D}} = \frac{[R] \times [D]}{K_D\left([R] + \frac{[R] \times [D]}{K_D}\right)}$$

$$= \frac{[R] \times [D]}{K_D[R] + [R][D]} = \frac{[R] \times [D]}{[R]\left(K_D + [D]\right)} = \frac{[D]}{K_D + [D]}$$

Q.E.D

والدكتور قال إن الـ Derivation ده معظم بيجي سؤال في الإمتحان

∴ We finally proved that :

$$f = \frac{[DR]}{[R] + [DR]} = \frac{[D]}{[D] + K_D}$$

طيب و بعدين ـــ إنت عايز إيه يعني صاحبنا زهقتنا .

(*) We can conclude that :

as $[D]$ (drug dose) increases → $\{f \uparrow\}$ → So response ↑

, as K_D (equil. dissociatn. const.) decrease → $\{f \uparrow\}$ → " " "

ماشي ـــ إقتنعنا بال point دي ـــ عايز تقول حاجة تانية ؟

(*) When $[D] = K_D$ → the drug will occupy 50% of the total receptors present.

ie// $f = \frac{[D]}{[D] + K_D} = \frac{[D]}{[D] + [D]} = \frac{[D]}{2[D]} = \frac{1}{2}$

∴ Drug occupies $\frac{1}{2}$ (50%) of total receptors

ماشي ـــ وال Point دي كمان شغالة.

طيب ـــ مهم ال Point دي عايزين نجيب تعريف لل K_D

علشان نجيب تعريف للـ K_D ← هنمشي بالعكس ← إزاي ؟

يعني هنقول ← لو عندنا $f = \frac{1}{2}$ (50%) ← يبقى أكيد الـ K_D
هتساوي الـ conc. بتاعت الـ free drug (D)

صح ولا أنا غلطان ؟

∴ $K_D = [D]$ when $f = 50\%$

∴ K_D (equilibrium dissociation const.) can be defined as:

"It's the conc. of free drug at which half of maximal receptor binding or fractional occupancy is observed"

ومن هنا ممكن نرجع الـ curve اللي قلنا إنه مهم وهنشرحه بالتفصيل بعدين

receptor bound drug
effect يعني الـ

50%

K_D

Conc. at site of actn.

وقلنا عليها مهمة وخليها في مخنا

طيب عايز تقول حاجة تانية عن الـ K_D ؟

آخر حاجة ← اقلب الصفحة

آخر حاجة بس الـ K_D

⊛ K_D is a constant that characterizes the receptor affinity for binding the drug in a Reciprocal fashion

كده بأنا نستهل ص إيه الكلام الفارغ ده ؟

→ This means that if K_D is ↑ ∴ f is ↓
∴ surely this drug has low affinity to receptors and Vice Versa. N.B K_D only have relation ē Affinity not potency or efficacy

ie// affinity $\propto \frac{1}{K_D}$ as may be drug have ↑ affanity but ē ↓ potency and efficacy.

وكده نبقى خلصنا الحتة الرخمة دى اللى مليانة equations
ـه تتمنى إنها تكون وصلت كويس
ـه لو هناك أى سؤال أو إستفسار ـه لا تتردد ـه تعالى وإسأل.

ودلوقتى نقول حاجة جديدة

Forces Binding the drug to Receptors

They may be :
1. Covalent bonds
or// 2. ionic bonds
or// 3. H - bonds
or// 4. hydrophobic force (apolar)
or// 5. Van der Waal force (dipolar)

وحاجة ثانية جديدة

Routes of Drug Administratn

[A] Enteral : → i.e. through the GIT

1) Oral : (as capsules, tablets)

- Most common, economical, safe.
- Most variable (differ according to physical characters, presence of food or other drugs, destruction by digestive enzymes or low gastric pH)
- Undergo first pass effect of portal circulation
- Villi of upper intestine provide an extremely large surface area.

2) Sublingual : → drug is placed under the tongue

* Drug pass through cappillaries network to systemic circulation
* Avoid metabolism in liver (1st pass effect) or intestine.

3) Rectal :

* About 50% of drugs given rectally avoid liver metabolism. [first Pass effect]

* Useful in patients with vomiting or unconscious (غائب عن الوعي) patients

* Unreliable absorption →
علشان في 50% من الادوية ممكن يحصلها 1st pass effect في الـ liver

* كده خلصنا اول route ← معلش هو كلام نظري بس كلها حاجات احنا عارفينها من قبل كده ↙
تانى نوع oooo

B Parentral :

(بيجي اجابة الدكتور اللي بيدي الحقنة)

* disadv. : risk of infection, pain & local irritation.

1) IV :

* Useful for poorly absorbed drugs that are soluble.
(soluble drugs → i.e. ionized → so not absorbed through the GIT (acts only on unionized drugs) but absorbed through IV injection)

* Avoid first pass metabolism through the liver.

* 100% absorption & immediate response.

* Problem of overdose treatment

يعني لو اخد العيان جرعة زيادة ← يلا السلامة ← مش هلحقه

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2) IM: (Intramuscular)

* For aqueous drugs → rapid response.
  or oily ones → depot release

* Vol. < 5ml (c.c.)

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3) Subcutaneous:

* It is slower and less hazardous (اقل خطورة) than IV

examples: + epinephrine with local anaesthetics (to prolong their duration)

+ Insulin.

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* ودول طبعاً اشهر اتنين routes هناك آخر حاجة وهي تشكيلة من routes تانية ooooo

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[C] Others:

1) Inhalation:

* For gaseous drugs (anaesthetics, antiasthmatics)

* Rapid onset of action.

2) Intranasal :

examples :

- Calcitonin hormone for osteoporosis
- Cocaine abuse .. تعاطي الكوكايين

3) Intrathecal : → injection into the CSF

* example : Methotrexate in case of leukemia

4) Topical : على الجلد من بره

as : Clotrimazole as antifungal (Local)

absorption يعنى يشتغل من بره بس ← ما يحصلوش اى

5) Transdermal :

as : Patches of nitroglycerin (systemic for ttt of angina)

كده خلصنا الجزء الشرح ده ← نشوف جزء جديد فى المحاضرة دى ....

بس الاول عايزين تفتكر سوا الـ def. بتاع الـ

Pharmakokinetics ...

حد فاكر ؟!!

* **Pharmakokinetics**: effect of body on drug [ADME]
  - absorption
  - Distribution
  - metabolism
  - Excretion

دلوقتي هنشوف واحدة واحدة من دول بالتفصيل الممل ....

[1] Absorption

* **Definition**:
It is the transfer of drug from the administration site to blood.

N.B.: For drugs to traverse cellular barriers (eg: GIT mucosa) → these drugs have to cross the lipid membrane.

يعني الدواء مثلاً عندي من الـ stomach وعايزاه يوصل للدم بيبقى طبيعي لازم نعدي من خلال الـ GIT mucosa يعني لازم يخرق يعبر من خلال الـ lipid memb.

طب هيعدي الـ memb. ازاي ؟!

* **Drugs cross lipid membranes mainly by**:

(A) Passive Diffusion:

depends on:
1) Conc. gradient (i.e. high → low conc)
2) Lipid solubility

* **Factors aff. Passive diffusion:**

↳ "Fick's Law"

a) Passive diffusion → directly prop. to SA of memb. (that's why upper intestine has very good absorption, also using syringe of small SA needle has better diffusion than one with large SA)

b) Passive diffusion → inversely prop. to the thickness of the memb.

N.B.: Majority of drugs use this method.

(B) Active Transport:

* ATP dependant (requires energy) ✓
* Against conc. gradient.
* Using specific carrier protein.

(C) Facilitated diffusion:

→ another carrier mediated transport

* without energy

example: - Insulin sensitive muscle cell glucose transporter
- P-glycoprotein efflux transporter.

الدكتور جمع كل انواع الـ transport في الجدول اللي جاي ده ....

Drug Transport across membranes

Mechanism	Energy	Carrier	Notes
• Passive diff.	No	No	ملحتاجناش هنزل تاني ... ذكرناه ده لوحده ... الجدول ده لما نستلم الكتاب
• Facilitated diff	No	Yes	
• Aqueous channels	No	No	
• Active transport	Yes	Yes	

• [Passive diffusion / Aqueous channels] — No Energy, No Carrier

• Active Transport — Yes Energy, Yes Carrier

• Facilitated Channels — No Energy, yes Carrier

* Effect of pH on drug absorption:

* Most drugs are either weak acids ($3 < pKa < 7$) or weak bases.

* drugs cross membranes more readily if they are uncharged & more lipid soluble.

* **Dissociation constant (pKa):**

________________ is the pH at which half of the drug is in ionized form.

* pKa is drug's acid dissociation constant.
* pKa is low for acids & high for bases (>7)

* To determine the uncharged absorbed portion of the drug:

لأن قلنا ان ده اللي بيحصل امتصاص

use "Handerson - Hasselbalch eqn".

~~pKa - pH = log un Ioni / Ioni~~

$$pKa - pH = \log \frac{[\text{protonated}]}{[\text{unprotonated}]}$$

~~[illegible] Ionized~~ ~~Ionized~~

Weak acids:

$HA \rightleftharpoons H^+ + A^-$

↙ unionized (protonated).

Weak bases:

$BH^+ \rightleftharpoons B + H^+$

↙ ionized (protonated)

(N.B) protonated form = unionized acids, ionized bases

Weak acids	Weak base
$pKa - pH = \log \frac{\text{unIonized form}}{\text{Ionized form}}$	$pKa - pH = \log \frac{\text{Ionized form}}{\text{unIonized ''}}$
$HA \rightleftharpoons H^+ + A^-$	$BH^+ \rightleftharpoons H^+ + B$

↓ unIonized (protonated)	• ↑pH → ↓H⁺ Rx forward → Ionized ↓absorptn	↓ protonated (Ionized)	↓pH → ↑H⁺ Rx Balkwork → Ionized → ↓absorptn

فى تعريف كده قاله الدكتور وهـــو:

* pH partition (Ion trapping): weak acids tend to accumalate in compartments of relatively high pH, while weak bases tend to accumalate in compartments of relatively low pH.

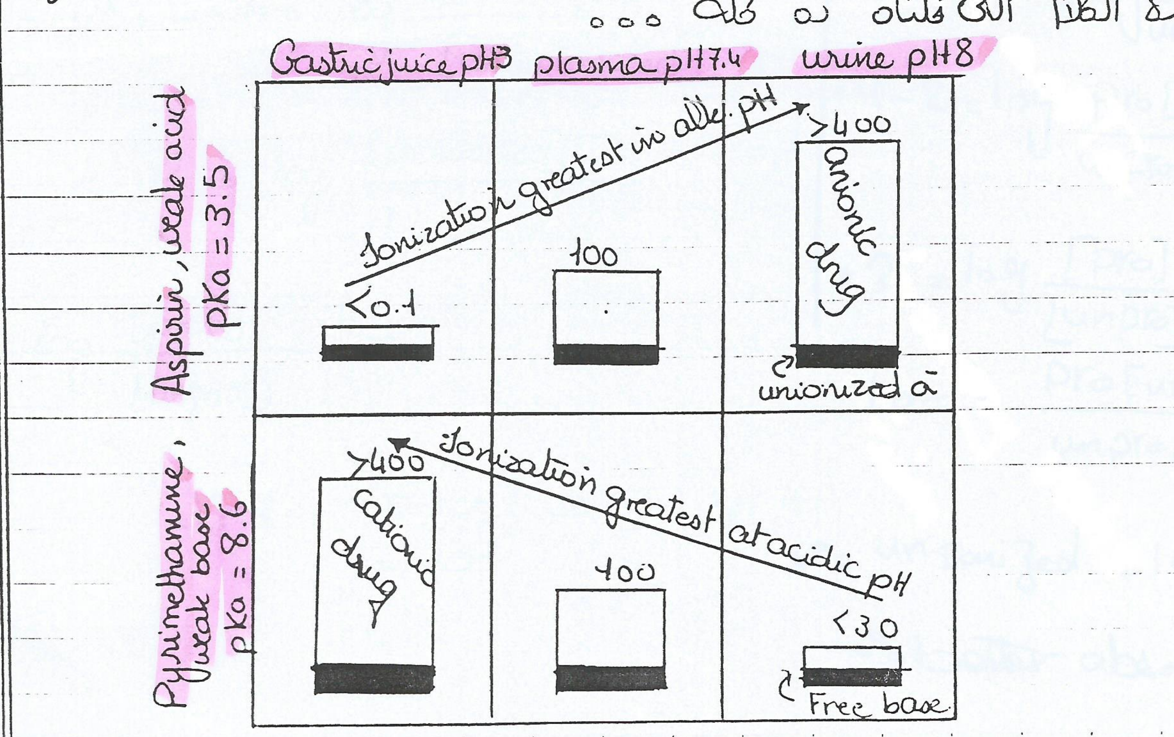
وده منطقى جداً لان لو بصينا مثلاً على الـ eq: بتاعت الـ weak base

$$BH^+ \rightleftharpoons H^+ + B$$

فى الـ low pH ← هيكون عندى H^+ كتيـر اوى فال reaction ده هيمشى backward فى اتجاه الـ BH^+ اللى هو الـ ionized form واحنا قلنا قبل كده ان اللى بيحصله absorption هو الـ unionized form ← يبقى ده مش هيحصله abs. يعنى هيحصله trapping او accumalation.

ونفس الكلام مع الـ weak a بس بالعكس ....

* طب تعالـوا نشـوف example وسالتين خفاف كده علشان نفهم فايدة الكلام اللى قلناه ده كله ...



Aspirin:

$$C_8H_7O_2COOH \rightleftharpoons C_8H_7O_2COO^- + H^+$$

$$HA \rightleftharpoons H^+ + A^-$$ weak a

Pyrimethamine:

$$C_{12}H_{12}Cl\,N_3NH_3^+ \rightleftharpoons C_{12}H_{11}Cl\,N_3NH_2 + H^+$$

$$BH^+ \rightleftharpoons B + H^+$$ weak b

Problem:

Aspirin ($pKa = 4$) at stomach (pH 2), will it be absorbed or not ?!

هنعوّض ببساطة في ال eq? ونشوف نسبة protonated : unprotonated
وبما ان ال aspirin ده weak acid يبقى ال protonated = unionized
وال unionized بيحصلها abs. احسن يبقى مفروض الاقى
ال protonated اكتر .... فوقوا !؟ تعالوا نحلها، هنلاقيهم
اكتر. .....

$$pKa - pH = \log \frac{[protonated]}{[unprotonated]}$$

$$4 - 2 = \log \frac{[protonated]}{[unp.]}$$

$$\log \frac{[prot.]}{[unprot.]} = 2$$

ايه الرقم اللى ال log بتاعه ب 2 ؟!
= 100

- $pKa - pH = \log \frac{prot.[unIoni.]}{un''[Ioni]}$
- $4 - 2 = \log \frac{pro[unIoni.]}{unpro[Ioni.]}$
- $2 = \log \frac{[pro]}{[unpro]}$

$$100 = \frac{pro[unIoni.]}{unpro[Ioni.]}$$

∴ unIonized = 100 Ionized

∴ better absorptn

$\therefore \frac{[\text{protonated}]}{[\text{unprotonated}]} = 100$

$[\text{protonated}] = 100\,[\text{unprotonated}]$

يبقى كمية الـ protonated الموجودة اد 100 مرة الـ unprot.

and as aspirin is weak acid
∴ protonated = unionized
↓ ∴ more lipophilic
∴ better absorption.

* يارب كله تكونوا فهمتوا ... لو في حد لسة مش فاهم ، ييجي اشرحاله بس مهم اوي تكونوا فاهمين الكلام ده ...

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* Problem:

انا لو عندي دواء عايزه يشتغل في الـ kidney واحنا عارفين الـ pH بتاعة الـ urine بـ 8 ... يعني انا عايزه يشتغل في الـ kidney يبقى مش عايز يحصله reabsorption من الـ renal tubules

* Will I use urine acidifying drugs or alkalinizing drug ?!

اوعوا تتخضوا ... هي فكرتها سهلة اوي وزي اللي فوق
تعالوا نشوف هنحلها ازاي ؟!
هنجرب الأول الـ urine acidifier ولنفرض الـ pKa = 4

in Case of using Acidifying drugs.

$$\log \frac{[prot.]}{[unprot.]} = pKa - pH$$

$$= 4 - 8$$

$$= -4$$

تقلبها علشان نشيل الـ -ve

$$\log \frac{[unprot.]}{[prot.]} = 4$$

$$\frac{[unprot.]}{[prot.]} = 10^4$$

∴ [unprot.] = 10^4 [prot.]

i.e. unprotonated > protonated

and this case is weak acid

↓

i.e. protonated = unionized.

↓

i.e. ionized > unionized

& ionized is poorly absorbed

وده اللى انا عايز اعمله ...

∴ We use weak acidic drug to acidify urine and trap the drug (for ex: high dose of basic drugs)

∴ pKa − pH = log $\frac{pro.}{unpro.}$

$$8 - 4 = \log \frac{pro.}{unpro.}$$

$$4 = \log \frac{unpro.}{pro.}$$

$$\frac{unpro.}{pro.} = 10^4$$

unpro. = 10^4 pro

∴ unpro. > pro.

∴ Ionized > unIonized

∴ ↓ absorptn

∴ We use acidic drug To acidifying urine and Trap b.Drug.

N.B: Although Aspirin is an acidic drug (should be better absorbed from stomach) → it is absorbed more from the intestine due to high surface area of microvilli

احنا كدة خلصنا تحت العنوان بتاع الـ Absorption ...
هنشوف فيه نقطة جديدة وهي ...

Factors Affecting Absorption

* 75% of the drugs taken orally are absorbed within 1 → 3 hours.

1) Blood flow to the absorption site:

blood flow in the intestine is greater than the stomach
∴ absorption at the intestine is better.

2) Total Surface area available for absorption:

we mentioned before that the SA of intestine is very high (about 1000 times that of the stomach due to microvilli)

∴ Absorption across the intestine is more efficient.

3) Contact time at the absorption site:

- Better absorption takes place in empty stomach with faster gastric emptying.
- Presence of food in the stomach → dilutes the drug & slows gastric emptying
- In case of severe diarrhae (the drug moves through GIT very rapidly) → not well absorbed.
- Anything that delay transport of drug from stomach to the intestine → delays rate of drug absorption.

4) Physicochemical factors:

eg: - liberation from formula
- chelation
- pka
- solubility, ---- etc.

دى تعريفين كده بس الدكتور ماقلهمش فى المحاضرة ...
اعرفوهم ... هما سهلين ...

* **Bioavailability**: It is the fraction of unchanged drug that gains access to the systemic circulation after administration by any route, eg: oral.

يعنى ببساطة كمية الدواء اللى هتوصل للـ systemic circulation
علشان تدين تأثير

↓ Bioavailability → systemic circulation

by 1 ↓ absorption
2 1st Pass effect

oral Antibiotic 100mg in blood 1mg
IV " 1mg

 ∴ 100mg at. is Bioequivalent to 1mg I.V

* Bioequivalence: Implies that if one formulation of a drug is substituted for another, No clinically untoward consequences will result.

يعني لو بدلت الدواء بتاعي بدواء تاني ← يدين نفس التأثير بالضبط

احنا كل ده كنا بنتكلم عن ال absorption
اللى هى اول واحدة فى ال (ADME) بتاعة الـ pharmacokinetics
فاكرين !!؟ (look p. 15)

تعالوا نشوف تاني حرف ال D ....

2 DISTRIBUTION

* Definition: The process by which a drug reversibly leaves the blood stream and enters the interstitial (extra cellular) fluid and/or cells of the tissue

يعني فى ال absorption الدواء عدى من المكان اللى اديته فيه للدم
لكن فى ال distribution هيتوزع بقى من الدم للخلايا علشان يدين التأثير المطلوب

* Factors affecting delivery of a drug from the plasma:

(Factors aff. distribution of drug)

A Blood flow: أكيد المكان اللى فيه blood flow عالى هيتوزع الدواء فيه اسهل واسرع

blood flow to brain, liver & kidney > muscles & fat.

B Capillary Permeability:

determined by:

1 Capillary structure:

eg: BBB (Blood Brain Barrier) where capillaries are continois with tight intercellular junctions

زى ما اخدنا فى ال Biopharmaceutics ان المخ خلاياه مقفولة بال tight junctⁿ

دى علشان مفيش حاجة غريبة تقدر توصل لل CNS

∴ Only lipid soluble drugs can cross it, while polar drugs cannot.

- Drugs can also pass through "Active Transport".
- In contrast to that, are capillaries of liver & spleen.

2 Drug structure:

- lipid soluble (Hydrophobic) drugs can readily pass through the membrane

While, hydrophilic drugs, polar, with non uniform electron distribution → can't cross the membrane & pass through slit junction →

خداناها فى ال Bio برده ، هى عبارة عن فتحة صغيرة

فى الخلية يقدر الدواء يعدى منها لداخل الخلية.

Lipid

C Binding to plasma proteins:

انا عايز الدواء يروح من ال plasma للخلايا ، فلو هو جه
دسكلس في ال proteins الموجودة في ال plasma ، يبقى هيصعب
خروجه للخلايا .

i.e. binding to plasma proteins → ↓ diffusion of drugs from plasma.

طيب تعالوا نشوف حاجة جديدة ومن فضلكم فتحوا
مخكم معايا أوي في الحتة دي علشان نفهمها كويس وانا
هحاول ابسط السيا على قد مأقدر ....

** Apparent Volume of Distribution (Vd): **

هكتب ال def. كده حتة واحدة وبعدين هشرحه

* def.: It is the volume of plasma that would contain total body content of a drug at a concentration equal to that in the plasma.

* يعني ايه القرف ده!؟ نشرح شوية عربي
الاول لازم نعرف أن ال Vd ده حاجة
تخيلية او افتراضية hypothesis علشان تحدد لي اذا كان الدواء
اللي اخدته وصل للمكان اللي انا عايزه في الجسم وبال conc. اللي
هتدين ال effect ولا لأ ، مع العلم ان الدواء لما بيتاخد بيتوزع
في حتت كتيرة اوي في الجسم هنعرفها بعد شوية من ضمنها
المكان اللي هيدي فيه ال effect.

* Following absorption into the blood stream, a drug distributes into interstitial & intracellular fluid.

* طيب انا لازم الاقى الدواء (بعد ما يروح فى حتت كتيرة فى الجسم) ب conc. معينة فى ال plasma علشان يقدر يدينى التأثير المطلوب

يعنى لو اخدنا دواء 500 mg ولما جيت اقيس كميته فى ال plasma لقيتها 0.1 mg بس وانا عارفة انه علشان يدى تأثير لازم تكون ال conc. اللى فى ال plasma = 0.5 mg ، يبقى انا لازم اديله جرعة أكبر من الدواء ده ...

$$Vd = \frac{D}{C} \quad \text{or} \quad C = \frac{D}{Vd}$$

- Vd → volume of distribution (constant parameter of each drug).
- D → Dose (total amount of drug in the body)
- C → conc. of drug in the plasma.

* كل ما ال value بتاعت ال Vd بتزيد → ده معناه ان الدواء اتوزع فى حتت كتيرة اوى فى الجسم وكميته فى ال plasma قليلة اوى.

* طيب انا ازاى هاستخدم دى فى الواقع علشان احدد كمية الدواء اللى اخده ويدينى ال effect المطلوب.

- we said that Vd → is constant for each drug.
- I'll give certain dose of the drug & measure its conc in the plasma → C_1 (initial conc. in the plasma)

∴ $Vd . C_1$ = amount of drug initially in body.

- the conc. I need to find in the plasma = C_2 → ودى انا عارفاها بردو

∴ $Vd . C_2$ = amount of drug in body needed to achieve the desired plasma conc. → هو ده اللى انا عايزاه.

• The diff. bet. the 2 values $= Vd.C_2 - Vd.C_1 = Vd\,(C_2 - C_1)$

is the additional dosage needed

وهى دى الكمية اللى انا هاديها للمريض زيادة على الجرعة اللى بياخدها علشان اوصل لل conc. اللى انا عايزاها فى ال plasma (C_2) علشان اوصل للتأثير المطلوب .

وصلت ؟!!!

يارب ...

لو لسة موصلتش .. تعالوا اشرحهالكم ...

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* طيب احنا قلنا ان الدواء هيتوزع فى اماكن كتيرة فى الجسم ايه هى الاماكن دى؟ ....

المكان الاول واللى لازم يكون فى الدواء حتى لو بنسبة صغيرة هو ال plasma ... وكل ده بيتحدد حسب ال structure بتاعت الدواء

Water Compartments in the body & drug distribution

1) Plasma Compartment: كل الادوية لازم توصل لل plasma.

* if a drug has a very large M.wt
or
binds extensively to plasma proteins → thus is trapped within the plasma.

* example of drugs found only in plasma: Insulin, Heparin

---

2) Extracellular Fluid:
(Interstitial fluid)

الادوية دى هلاقيها فى:
plasma + extracellular fluid

* drugs have low M.wt but hydrophilic → ∴ they can move through the endothelial slit junctions of capillaries into the interstitial fluids but can't cross the membranes of the cells.

* Examples: Tubocurarine, Theophylline

---

3) Total Body Water:

دى هيجى كله فهلاقيه فى:
plasma + extracellular fluid + Intracellular fluid → يعنى هيعرف يعدى من كل حاجة ويدخل جوه الخلية

* if the drug has low M.wt and lipophilic → ∴ it can move also intracellularly into the cell.

* Example: Ethanol, phenytoin & Paracetamol.

طب سؤال كده على الماشى ... ياترى مين فى ال 3 compartments اللى قلناهم فوق دول هيبقى عنده اعلى Vd ؟!
فكروا شوية كده ....
انا هساعدكم واقولكم ان ال Vd هو كمية الدواء المتوزع فى الجسم divided by كميته فى ال plasma ...
ها عرفتوا ؟!
طبعاً ال total body water هتبقى اعلى Vd لانها اكتر واحدة متوزعة فى الجسم.

$$Vd = \frac{\text{Amt. of Drug distributed on body}}{\text{" " " in plasma}}$$

Page (31) → هنسأل سؤال مهم وجاء في الإمتحانات
ولو فاهم الحتة بتاعت ال Vd كويس هتحله ببساطة.

→ if you have 2 cases of drug toxicity :
1st Case → Toxicity with drug having high Vd
2nd " → " " " Low Vd

→ which one can be treated easier by blood dialysis (غسيل الدم) ?

يعني أنا لو غسلت دم الإثنين ← مين اللي هيفوق ؟

Answer : Surely : The one with Low Vd will be treated easier by dialysis

Because → in case of drug with Low Vd → the drug is more concentrated in plasma
∴ by plasma dialysis → we get rid a great amt. of the drug → treating the toxicity easily.

But → in Case of drug with ↑ Vd → the drug is distributed in different body compartments → not only plasma
∴ by plasma dialysis → we get rid of a small amt of the drug → ∴ small effect on treating toxicity

لو موصلتش ← تعالوا و إحنا نفهمها لكم.

N.B:

Binding of drug outside the plasma compartment

or

Partitioning into body fat يعني الدواء يروح لل fat اللى فى الجسم

↓ Vd of fat > Vd of body water

↑ Vd beyond total body water

وده طبعاً منطقي جداً لان الدواء مش هيتوزع بس على الـ fluids اللى فى الجسم لكن كمان فى شحوم هيروحوا يتخزنوا فى الـ fats اللى فى الجسم

يبقى طبيعى ان الـ Vd تتزايد اوى وتبقى اعلى من الـ total body water

* Examples of drugs undergoing this mechanism:

digoxin, morphine, tricyclic antidepressant.

بس خلاص .. خلصنا الجزء الفقيح ده ...

وصح آخر حاجة في المحاضرة العظيمة دي oooo

Plasma Protein Binding

* Drug molecules may bind to plasma proteins usually albumin.

Bound form ⇌ Free form.

Bound form → pharmacologically inactive

Free form → only free drug can act on target sites in tissues, produce response

* The Binding to albumin is reversible with varying affinities, may show low or high capacity

affinities → يعني قابلية الدواء علشان عسيك فيه

capacity → (n° of drug molecules binding to single albumin molecule)

* albumin has strongest affinity for anionic drugs (weak acids) & hydrophobic drugs

* الدكتور وقف هنا وهنكمل الموضوع ده المحاضرة الجاية.
* معلش هي المحاضرة طويلة شوية بس مش بإيدينا.

The Last & most imp. request oooo
pLZ ooo Pray 4 us a Lot ooo.

Plasma Protein Binding (PPB) ← في آخر صفحة في المحاضرة الثانية
← هنزود بعض الكلام في السريع كده.

Drug in plasma :
- → Bound to plasma proteins
  ∴ indiffusable → ∴ inactive.
- → Free drug in plasma
  ∴ diffusable → ∴ active

→ The most Famous protein in plasma is **Albumin**

→ Albumin has 2 sites :
- → ① for acidic drugs
  * has Low capacity But high affinity.
- → ② for Basic drugs
  * has high capacity But Low affinity.

Drugs

class I	class II
effective when free in small percent 1% for example	effective only when ↑ percent is free 40% for example.
• free drug 1% / bound drug 99%	bound drug 60% / free drug 40%
example : tolbutomide drug for insuline release, glucose regulatn	example : Sulfonamide

→ class I drugs → if displacement interaction occurs another percent of bound drug becomes free giving a toxic effect

يعني إيه ؟

← يعني لو أى drug له affinity للـ plasma proteins أكتر من الـ drug اللى أصلاً ماسك ← هيدخل مكانه ويعمل release للـ drug اللى هو كان ← effective بـ small percent (1%) ← فالـ free percent هتزيد تبقى مثلاً 2% ← كده نبقى ضاعفنا الـ dose ويبقى الـ drug ← Toxic.

∴ displacement interaction here is dangerous.

→ Danger of displacement interaction :
1. decreases as Therapeutic index increases. [TI↑]
2. " as V_d ↑ "

كده ← المحاضرة التانية تبقى تمام.

Lecture ③ زيادات على

هنرسم رسمة علشان نوضح تحول الـ drugs بالـ metabolism ممكن يكون عامل ازاى

Lipophilic drug	→ Liver →	hydrophilic drug
active drug	→ Liver →	inactive drug.
active drug (codein)	→ Liver →	more active drug (morphine)
inactive drug (prodrug) (Metronidazole)	→ Liver →	active drug.
active drug (Paracetamol)	→ →	toxic metabolites.